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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/508,898	09/23/2004	Linda L. Brockunier	21070YP	3656

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EXAMINER	
LOEWE, SUN JAE Y	
ART UNIT	PAPER NUMBER
1609	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,898	BROCKUNIER ET AL.	
	Examiner	Art Unit	
	Sun Jae Y. Loewe	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 21-41* is/are rejected.

7)☒ Claim(s) *20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/23/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on September 23, 2004 was in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. Accordingly, the information disclosure statement was considered. A signed copy of form 1449 is enclosed herewith.

Abstract

2. Although this application contains an abstract of the disclosure as required by 37 CFR 1.72(b), an abstract on a separate sheet is required.

Claim Objections

3. Claim 20 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-19, 21-41 are rejected under 35 USC 112 1st paragraph as failing to comply with the written description requirement.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

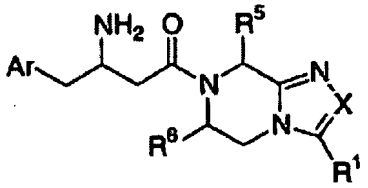
The MPEP states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The Guidelines for Examination of Patent Applications Under 35 USC 112, ¶1, "Written Description" Requirement (Federal Register, Vol. 66, No. 4, pg. 1105, column 3), in accordance with MPEP § 2163, specifically states that for each claim drawn to a genus the written description requirement may be satisfied through sufficient description of a representative number of species by a) actual reduction to practice; b) reduction to drawings or structural chemical formulas; c) disclosure of relevant, identifying characteristics (ie. structure) by functional characteristics coupled with a known or disclosed correlation between function and structure. The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention (Federal Register, Vol. 66, No. 4, p. 1105, 3rd column, 3rd paragraph). Below is such comparison.

It is noted that in the following the comparison is focused on the *compounds* of formula I. It is to be understood, however, that a *prima facie* conclusion of lack of written description for product implies the same conclusion for the process of use. In other words, the process of use cannot be practiced in absence of the product.

Scope of Claims 1-19, 21-41:

The claims are drawn to product or method of using product containing compound of formula I (below).



The variables to formula I are defined broadly and generically (definitions in claim 1; X = CR^2/N; Ar = phenyl substituted with R^3), except:

a) Claims 7, 12, 13: scope of R^1 is narrow/congruent with scope of disclosure

b) Claims 3-5: R^2 is absent because X = N

c) Claim 16: scope of R^2 is narrow/congruent with scope of disclosure

d) Claims 8, 9: scope R^3 is narrow/congruent with scope of disclosure

e) Claims 5, 18, 19: scope of R^5 is narrow/congruent with scope of disclosure

f) Claims 4, 7, 18, 19: scope R^6 is narrow/congruent with scope of disclosure

Scope of Disclosure

Reduction to Practice:

The compounds reduced to practice (examples 1-30 in the specification) belong the following subgenus:

a) R^1: H, CN, C_{1-10} alkyl optionally substituted with 1-5 halogen

b) R^2: H, CN, C_{1-10} alkyl optionally substituted with 1-5 halogen

c) R^3: halogen

d) R^5/R^6: H, C_{1-10} alkyl (*not* substituted with naphthyl or $CONR^7R^8$), phenyl (optionally substituted with halogen or C_{1-6} alkyl), CO_2H or CO_2C_{1-6}alkyl

Reduction to Structural or Chemical Formulas:

The only disclosure, in addition to the species reduced to practice, is in form of *lists* of possible substituents for each variable. This type of disclosure is not viewed to be a representation of any of the species it entails. A"laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. MPEP 2163.I.A. and *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

Therefore, there is no disclosure of species in addition to those reduced to practice (eg. by reduction to structural/chemical formulas).

Correlation between Structure and Function:

A correlation between structure and function, for the instantly claimed genus of compounds, is neither disclosed nor commonly known in the art. Thus, it is not known what *specific structural elements* are *essential* for the activity of the instantly claimed compounds as DPP-IV enzyme inhibitors.

Analysis of Fulfillment of Written Description Requirement:

The predictability in the art is low. A structure/activity relationship determined for a series of N-isoleucylthiazolidide inhibitors of the DPP-IV enzyme afforded that changing the size or nature of the substituent(s) to the 5-membered ring affected potency. Similar structure/activity relationship was determined for a series of pyrrolidine-2-nitrile inhibitors of the enzyme. See Augustyns et al., p. 501, 2nd column. Generally, activity of an inhibitor is dependent of the interactions of specific groups/moieties in the structure with amino acids in the enzymatic active site (see for example, Augustyns et al., p. 501, 2nd column). For the genus of compounds claimed, it is unknown what structural features are involved in these specific interactions. Thus, the skilled artisan is unable to foresee whether any of the claimed compounds, excluding the subgenus reduced to practice, will possess DPP-IV inhibiting activity.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention. The specification *prima facie* lacks written description beyond the *subgenus* represented by the *compounds reduced to practice*.

5. Claims 1-19, 21-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling the skilled artisan to make and use the subgenus of products reduced to practice, does not reasonably provide enablement for the use of products claimed that fall outside of this subgenus.

Additionally, the specification is *enabling* for:

(a) a method of inhibiting DPP-IV enzyme activity in a mammal. Reasonable correlation between in vitro and in vivo DPP-IV inhibiting activity has been shown in the art (eg. Augeri et al., p. 5028, Table 1);

(b) a method of ameliorating or reducing the risk of atherosclerosis and lipid disorder when using product of formula (I) in combination with HMG-CoA (Erez et al., abstract);

(c) a method of ameliorating or reducing the risk of diabetes (Augeri et al, p. 5025, 1st paragraph; McIntosh et al., p. 162, sections 3.2 and 3.2.2), insulin resistance, and low glucose tolerance (Augeri et al., p. 5026, 1st column, 2nd paragraph) using product of formula (I);

(d) a method for ameliorating or reducing the risk of obesity (Rieusset et al., abstract), hyperlipidimea (He et al., page 15717, 1st column, 5th paragraph), hypertension (Ryan et al., abstract), and impaired glucose tolerance (Hung et al., abstract), in addition to the conditions stated in (c) when using product of formula (I) in combination with the products noted in claim 31

Additionally, the specification is *not enabling* for:

(e) the preparation of a pharmaceutical composition for "treating" (ie. prevention and prophylaxis, see definition in p. 16 of specification) atherosclerosis (see claim 38). It is noted that a specific definition for "prophylaxis" was not provided in the specification. Thus, the art recognized definition, "the preventing of a disease", was applied herein for the purpose of this examination (http://dictionary.reference.com/browse/prophylaxis/p.1). The term "treating" as used heretofore is intended to mean prevention/prophylaxis to be consistent with the definition by the Applicant.

(d) a method for "treating" of *any* of the conditions disclosed in the specification;

(e) a method for ameliorating or reducing the risk of the diseases not stated in (c) and (d) using product of formula (I), alone or in combination with other active ingredients;

In conclusion, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

(Claims 1-19, 21, 38, 40, 41: Product)

The breadth of the claims

(1) The claims are drawn to products of Formula I with the scope as defined in section 4, supra.

(2) Claim 38 is drawn to a pharmaceutical composition specifically for "treating", ameliorating, reducing the risk of atherosclerosis using product of formula (I) in combination with HMG-CoA reductase inhibitor.

The nature of the invention
The genus of compounds are claimed to possess DPP-IV inhibiting activity. No additional utility is disclosed.

The state of the prior art/level of ordinary skill/level of predictability
(1) The level of ordinary skill is high, but the level of predictability in the art is low. There is no art known correlation between structure/function for this class of compounds. Therefore, one of ordinary skill would not know which of the compounds within the claimed genus, excluding the subgenus of compounds reduced to practice, would possess DPP-IV inhibiting activity.

(2) It is commonly known in the art that HMG-CoA inhibitors (statins) are potent lipid lowering drugs, which have been shown to reduce morbidity and mortality in patients with atherosclerosis (Erez et al., abstract). However, statins have demonstrated risk reduction of only 25-40% in clinical trials with a substantial proportion of treated patients retaining an elevated risk and experiencing cardiovascular events (Chapman et al., p. 894, 1st paragraph). Thus, a method of "treating" atherosclerosis using statins, or other medications, has not yet been elucidated.

The amount of direction provided by the inventor/existence of working examples
(1) The specification provides the disclosure of 30 compounds, reduced to practice, which were moreover tested to possess DPP-IV inhibiting activity.

(2) No direction is provided in the specification to enable the skilled artisan to solve the problem at hand, namely, the "treatment" of atherosclerosis.

The quantity of experimentation needed to make or use the invention
(1) The specification does not teach one of ordinary skill how to use the invention outside of the scope defined by the subgenus of compounds reduced to practice.

(2) The specification also does not teach now to make and use a pharmaceutical composition for the "treatment" of atherosclerosis.

The skilled artisan is unable to use the invention commensurate in scope with the breadth of the claims without first making an inventive step. The amount of experimentation needed is deemed undue.

(Claims 22-37, 39: Method of Use)

Note: The discussion below is directed to the enablement of the method of use in the circumstance where the starting material (ie. product of formula I) is available and known to possess DPP-IV inhibiting activity. For products outside of this genus, the methods lack enablement (see section 4).

The breadth of the claims
The claims are drawn to the method of "treating", ameliorating, or reducing the risk of a multitude of diseases including diabetes (1 and 2), low/impaired glucose tolerance, hyperglycemia, obesity, insulin resistance, hyperlipidemia, atherosclerosis, retinopathy, lipid levels, hypertension using compounds of formula (I), either alone or in combination with other active components.

The nature of the invention
Compounds of formula I are disclosed to possess DPP-IV inhibiting activity.

The state of the prior art/level of ordinary skill/level of predictability
The diseases for which art recognized correlations exist between amelioration/risk reduction and DPP-IV inhibition have been noted above. The discussion herein pertains to facts that suggests a lack of correlation between the "treatment"/amelioration/risk reduction of the remaining diseases and DPP-IV inhibition. The discussion below does not cover all the diseases disclosed; however, similar arguments apply to the conditions not specifically discussed. It is further noted that the discussion drawn to the "treatment" of diseases applies to methods which employ active components in addition to compounds of formula (I) – eg. claim 31.

Atherosclerosis:
- Amelioration/risk reduction by DPP-IV inhibition:
  - There is no art recognized method
  - There are multiple etiological pathways and causes (eg. advanced age, smoking, sedentary lifestyle, elevated serum levels of homocysteine and uric acid, stress, hypothyroidism) – see http://en.wikipedia.org/wiki/Atherosclerosis, p.1-3 of 3 – thus inhibition of one possible factor is not predicative of efficacy
- Prevention by medication is not recognized in the art

Diabetes:
- Prevention of diabetes 1 is to date not possible
- Prevention of diabetes 2 is possible through medication *in combination* with diet, exercise, and healthy lifestyle
- (http://diabetes.webmd.com/guide/preventing-type-2-diabetes)

Hyperglycemia:
- Because it is not otherwise defined, hyperglycemia is taken to encompass both the diabetic and non-diabetic forms

- Although diabetic hyperglycemia may be ameliorated by DPP-IV inhibition (Ahren et al., p. 2081, 2nd column), the non-diabetic form has a different mode of action (for example, binge eating in bulimia nervosa) and thus requires a different type of treatment (http://en.wikipedia.org/wiki/hyperglycemia, pg. 2 of 4)
- Prevention of diabetic hyperglycemia, which is primarily a symptom of diabetes, would require the prevention of the underlying diabetes, which is not known to be preventable by administering medication (http://en.wikipedia.org/wiki/Hyperglycemia, pg. 1-2 of 4)

Obesity and Lipid Levels (LDL, HDL):

- In clinical trials of DPP-IV inhibitors, participants displayed little or no change in body weight/lipid levels (Wiedeman et al., p. 145, Table 1).
- Results are suggestive of a *lack* of a nexus between DPP-IV inhibition and amelioration/risk reduction/prevention of disorders due to body weight (obesity) and lipid levels
- Further, it is well accepted that the use of medication alone does not prevent obesity; the amount of calories burned must exceed the calories taken in (http://www.webmd.com/diet/tc/Obesity-Overview)

Retinopathy:

- Because it is not otherwise defined, retinopathy is taken to encompass types (http://en.wikipedia.org/wiki/Retinopathy, pg. 1 of 2), not merely the diabetes induced form
- The mode of treatment varies depending on the cause; it is not expected that DPP-IV inhibition will ameliorate/reduce risk of all forms of retinopathy (eg. due to sickle cell anemia)

Insulin Resistance:

- Prevention of insulin resistance is possible through living a healthy lifestyle (http://diabetes.webmd.com/guide/insulin-resistance-syndrome)

Hypertension:

- Prevention may be achieved by maintaining a healthy weight, getting exercise, reducing salt intake and reducing stress (http://www.webmd.com/hypertension-high-blood-pressure/guide/preventing-high-blood-pr...)

The amount of direction provided by the inventor/existence of working examples

The disclosure provides a method of preparing compounds of formula (I). The disclosure further provides a subgenus of 30 compounds that were tested and thus are known to possess DPP-IV inhibiting activity.

The quantity of experimentation needed to make or use the invention

Based on the discussion above, the skilled artisan would be unable to practice the invention commensurate with the scope of the claims without first making a substantial inventive step. The quantity of experimentation needed is deemed undue.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. The term "controlling" in claims 23-37 and 39 is a relative term which renders the claim indefinite. The term "controlling" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. First, it is not clear what is meant by the term as applied towards a disease or condition. A multitude of meanings can be envisioned, for example, lessening the symptoms, delaying the onset, etc. Second, given a precise meaning for the term, it is still unclear as to what degree or against what standard the "control" is measured. This claimed limitation was not examined herein because the meaning could not be delineated.

Allowable Subject Matter

7. The subject matter encompassed by claim 20 is allowable for the following reason. The closest prior art is taught by Edmondson et al. in US 6,699,871. The core structure shared by the compounds is the same as that taught by the instant claims (formula I, see section 4). The prior art, however, teaches *only* a subgenus of compounds ($R^5 = R^6$ = hydrogen) that is excluded from the instant claims via a proviso. Thus, the compounds taught by Edmonson et al. neither anticipate nor make obvious the instant invention.

Conclusion

8. No claims are allowed.

9. Any inquiry concerning this communication should be directed to Sun Jae Y. Loewe whose telephone number is 571-272-9074. The examiner can normally be reached on Monday through Friday from 7:30 am to 5:00 pm.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Cecilia Tsang (571) 272-0562, can be reached. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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